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MEETING**

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COMMISSION ON HUMAN MEDICINES

PAEDIATRIC MEDICINES EXPERT ADVISORY GROUP

Title of paper: Persistent sexual dysfunction after discontinuation of Fluoxetine- data and proposal for a variation from the MAH

Type of paper: For Advice

Products(s): Prozac	Assessor:
Active constituent(s): fluoxetine	Previous Assessments: N/A
MAH(s): Lilly	Legal status: POM
Therapeutic classification: Antidepressants	

1.0 PURPOSE

The issue of persistent sexual dysfunction occurring after discontinuation of SSRI medications was previously discussed at the PEAG in November 2009. The Marketing Authorisation holder (MAH) for fluoxetine was asked to submit a review of all of their data relevant to the issue of persistent post SSRI Sexual Dysfunction (PSSD). The data were received in November 2010.

This paper considers the evidence submitted by the MAH that fluoxetine may cause sexual dysfunction that persists after ceasing the medication and considers the implications of the proposal of the MAH to submit a variation to include the risk of persistent sexual dysfunction on stopping fluoxetine in section 4.8 of the fluoxetine SPC.

2.0 BACKGROUND

The evidence for an association of PSSD with all SSRIs was discussed at the November meeting of the PEAG in 2009 (Annex I) and a decision was made to ask the MAH for fluoxetine for a cumulative review of adverse reactions related to sexual dysfunction suspected to be associated with fluoxetine use, with a particular focus on those cases that have persisted long term after treatment with fluoxetine has been stopped. It was agreed for the purposes of the review that the term "persistent" should be interpreted to mean at least 3 months after discontinuation of fluoxetine treatment, which is based on the half-life of fluoxetine and its active metabolite, norfluoxetine.

Section 4.8 of the current fluoxetine Summary of Product Characteristics (SPC) lists "Reproductive disorders: *Sexual dysfunction* (delayed or absent ejaculation, anorgasmia), priapism, galactorrhoea."

The Core Data Sheet (CDS) of fluoxetine states the following:
"Reproduction System and Breast Disorders: ejaculation disorder (including ejaculation failure, ejaculation dysfunction, premature ejaculation, ejaculation delayed, retrograde ejaculation), erectile dysfunction, gynecological bleeding, priapism, sexual dysfunction."

Section 4.8 of the United Kingdom SPCs of other SSRIs such as citalopram, sertraline, paroxetine, escitalopram, or fluvoxamine also state some undesirable effects on the reproductive system but the exact terms contain vary between products but generally reflect the terms sexual dysfunction, erectile dysfunction, decreased libido, hyperprolactinaemia, galactorrhoea but none of them are reported as persistent or prolonged after discontinuation (see Annex II).

The exact mechanisms for persistent sexual side effects after discontinuation of SSRIs as discussed in the literature provided by the MAH are unclear. Some theories report the effect of SSRIs on the negative feedback regulation of the hypothalamopituitary-testicular axis that may not fully normalize in some patients on ceasing SSRIs. Other papers discuss peripheral changes due to inhibition of serotonin receptors in the peripheral nerves, neurological alterations in the areas of the nervous system

responsible for sexual arousal and functioning and structural changes to brain regions involved in sexual response. Epigenetic changes caused by SSRIs are also postulated to be a mechanism of persistence of effect. (Csoka and Shipko 2006; Csoka et al. 2008).

Preclinical studies of all the SSRIs with the exception of sertraline show some association with adverse effects on reproduction in animals. Section 5.3 of the fluoxetine SPC summarises the evidence for a permanent effect of fluoxetine on the reproductive system in animals. In a juvenile toxicology study in CD rats, administration of 30mg/kg/day of fluoxetine hydrochloride on postnatal days 21 to 90 resulted in irreversible testicular degeneration and necrosis, epididymal epithelial vacuolation, immaturity and inactivity of the female reproductive tract and decreased fertility. Delays in sexual maturation occurred in males (10 and 30mg/kg/day) and females (30mg/kg/day). The significance of these findings in humans is unknown.

Sexual dysfunction is also common in people with the underlying indications for SSRI treatment. In 132 patients with depressive disorders, loss of sexual interest, characterised by loss of libido or decrease of sexual desire or potency, was reported by 72% of patients with unipolar depression, and 77% of patients with bipolar depression.¹

Post SSRI Sexual dysfunction (PSSD) is a term that has been introduced by an American psychologist from Iowa.^{2,3} It is a term that is not officially recognised by any medical dictionary. The term is widely referenced on internet sites..

Post-SSRI sexual dysfunction is defined on Wikipedia as ‘an iatrogenic type of sexual dysfunction caused directly by the previous use of selective serotonin reuptake inhibitor (SSRI) antidepressants. While apparently uncommon, it can last for months, years, or sometimes indefinitely after the discontinuation of SSRIs. It may represent a specific subtype of SSRI discontinuation syndrome.’

In this report, all available data sources on the association between the use of fluoxetine and the persistence of sexual side effects after ceasing the medication is considered.

3.0 The Data

3.1 Cumulative Review of Spontaneous Adverse Event Reports of Persistent Sexual Dysfunction

This review submitted by the MAH is focused on suspected adverse reaction reports concerning sexual dysfunction that persisted at least 3 months after discontinuation of fluoxetine therapy. The review includes serious and non-serious spontaneous reports from HCPs, patients and regulatory authorities along with published literature reports for the reporting period of 01 January 1983 through 30 September 2010.

The cumulative number of patient exposures to fluoxetine worldwide since first approval on 07 September 1986 through 31 August 2010 is estimated to be approximately 78.3 million patient-years.

The initial search of the Lilly Safety Database returned 4731 unique cases of which 1146 reported a Drug Stop Date. The Drug Stop Date was used to establish a reference baseline for determining whether an event was still occurring at 90 days after the end of fluoxetine therapy.

The Drug Stop Date was then compared with either : (1) Case Creation Date, (2) Event End Date, (3) Event Entered Date, or (4) Follow-Up Received Date (based on availability of information) to screen for events that potentially started or persisted 90 days or longer after fluoxetine administration was stopped.

These date comparisons returned 417 unique cases which were then reviewed manually to identify those cases describing sexual dysfunction events which could be confirmed as continuing for 90 days or longer following discontinuation of fluoxetine administration. This manual review process returned a total of 93 cases meeting the criteria of the search strategy comprising of 130 events.

Table 1. Number of Persistent Sexual Dysfunction Events by Preferred Terms Preferred Term(s) Number of Events Reported

Preferred Term(s)	Number of Events Reported
Erectile dysfunction	35
Libido decreased	25
Sexual dysfunction	17
Anorgasmia	14
Loss of libido	11
Ejaculation disorder	6
Priapism	5
Orgasm abnormal	4
Disturbance in sexual arousal	3
Ejaculation failure	3
Ejaculation delayed	2
Male sexual dysfunction	2
Libido increased	1
Orgasmic sensation decreased	1
Premature ejaculation	1
Total	130

Of these 93 cases, 85 were reported spontaneously, 7 were reported from regulatory authorities, and 1 was reported from the published literature. No serious adverse events were identified from clinical trials. The MAH confirm that 4 cases of erectile dysfunction, 3 cases of priapism, 2 cases of sexual dysfunction and 1 case of loss of libido were classified as serious but further details were not provided.

Among the 93 cases, 45 were medically (that is, reported by an HCP) confirmed and the remaining 48 were not medically confirmed (that is, reported by non medical professional or consumer).

Only 8.5% (11 events) of the 130 events were considered serious.

3.1.2 Age and Gender

Of the 93 total cases, gender was specified for 92 (99%). There were 68 (74%) males and 24 (26%) females. Age was provided in 74 (80%) cases. The reported ages ranged from 15 years to 77 years of age. The mean age was 43 years and median age was also 43 years.

3.1.3 Medical History/Preexisting Medical Conditions

Medical history was reported in 37 of the 93 (40%) cases. Of these 37 cases, only 7 cases reported a history of preexisting sexual dysfunction prior to fluoxetine therapy.

Of the remaining 30, 8 cases reported other confounding past medical histories such as hypertension, hypercholesterolemia, diabetes, illicit drug use, and alcohol abuse. One case reported a past history of an "active sexual life" prior to starting fluoxetine.

The remaining 21 cases reported other various medical histories that include, but are not limited to, the following: bladder cancer, appendectomy, dermatitis, thyroid deficiency, Crohn's disease, human immunodeficiency virus (HIV) infection, and premenstrual syndrome.

3.1.5 Concomitant Medication Use

Concomitant medication use was reported in 43 (46.2%) of the 93 cases. Of these 43 cases, 12 reported concomitant use of other antidepressants, which consisted of venlafaxine, mirtazapine, trazodone, nefazodone, buspirone, nortriptyline, amitriptyline, clomipramine, amfebutamone and dosulepin.

A total of 8 cases reported concomitant use of benzodiazepine class of drugs, which consisted of alprazolam, clonazepam, lorazepam, clonazepam, and nitrazepam. Seven cases reported concomitant use of an antipsychotic and/or a mood stabilizer, which consisted of haloperidol, risperidone, chlorpromazine, levomepromazine, lithium, and valproate semisodium. Six reported concomitant use of cardiovascular class drugs such as propranolol, sotalol, atorvastatin, irbesartan, lisinopril, digoxin, niacin/lovastatin, triamterene/hydrochlorothiazide and warfarin.

The remaining 10 cases reported other concomitant drug use, which consisted of ranitidine, levothyroxine, warfarin, paracetamol, cannabis and several others.

3.1.6 Indication for Use

A total of 80 cases provided an indication for use for fluoxetine. The reported indications are detailed in Table 2 below.

Indication	Number of cases
Depression	58
Obsessive-compulsive disorder	6
Anxiety	3
Major depression	3
Asthenia	1
Bipolar I disorder	1
Bulimia nervosa	1
Dysthymic disorder	1
Ejaculation disorder	1
Menopausal depression	1
Migraine	1
Panic disorder	1
Post-traumatic stress disorder	1
Premenstrual syndrome	1
Total	80

Table 2: Indication for treatment with fluoxetine

In the case with the indication for use reported as ejaculation disorder, the patient experienced decreased libido and decreased testosterone while on fluoxetine. No medical history and concomitant medications were reported.

3.1.7 Fluoxetine Dosing

Of the 93 cases, 75 cases (81%) provided a fluoxetine daily dose; dose was unknown in the remaining 18 cases. Fluoxetine dose ranged from 5 mg/day to 80 mg/day.

The most commonly reported fluoxetine daily dose was 20 mg (53 cases; 71%); the second most commonly reported fluoxetine daily dose was 40 mg (7 cases; 9%) and the third most commonly reported fluoxetine daily dose was 30 mg (5 cases; 7%).

There is no obvious dose relationship with the majority of patients reporting a fluoxetine daily use of 20 mg.

3.1.8. Continued Antidepressant Drug Therapy

Among the 93 cases, 11 reported a continued use of antidepressant drug therapy even after fluoxetine had been discontinued. Information on the course of antidepressant therapy is briefly described below:

In two cases the patients were switched to unspecified antidepressants; in 6 cases the patients were switched to other SSRIs; in one case the patient was switched to a SNRI, and in two cases the patients were switched to other drug class antidepressants.

In all of the 11 cases, the sexual dysfunction event continued even after new antidepressant therapy was initiated.

3.1.9. Reporter Causality

An opinion of relatedness was provided for 44 (34%) of the 130 total events. Of the 44 events, **29 (66%) reporters felt the event was related to fluoxetine use**; 4 reporters felt the event was not related and/or not associated to fluoxetine use and reporter causality was unknown in 11 events.

Reporters did not provide an opinion of relatedness for 37 events. In the remaining 49 events, reporter causality was not assessed as the reporter was a consumer, other, or unknown.

Assessor Comments:

Medical history was reported in 37 of the spontaneous cases, of which 7 reported preexisting sexual dysfunction. Eight cases reported histories that could potentially affect sexual function (hypertension, diabetes, illicit drug use, depression.). Concomitant medication use was reported in 43 cases, of which 12 reported concomitant use of other antidepressant medications. Eleven cases reported a continued antidepressant drug therapy after fluoxetine had been discontinued. There was no obvious dose relationship with the majority of cases taking 20 mg daily. The spontaneous data, as reported, would appear to contain multiple confounders and do little to contribute to the clear understanding of the phenomenon of post SSRI sexual dysfunction. Importantly the length of time the reported sexual side effects have persisted from 90 days was omitted from the report. It is unclear whether there are any recoveries or whether the sexual side effects have truly persisted. The MAH has not made any attempts at targeted follow up of the cases reported to them.

Up until 21st Jan 2011 the total number of cases on the MHRA database of sexual dysfunction associated with SSRIs is now 1143.

The breakdown of these reports is as follows (this includes the responses to the targeted FU which have now changed category):

UNKNOWN whether the reaction continued after drug withdrawn	732
Reaction did NOT continue after drug withdrawn	157
Reaction continued after drug withdrawn and the recovery time is unknown	116
Reaction continued after drug withdrawn and the recovery time is known	138
Total	1143

From the fourth category (reaction continued after drug withdrawn and recovery time is known) time to recovery ranges between 1 day to 3 months, the average time to recovery is 10 days and mean is 5 days.

From the third category (reaction continued after drug withdrawn and recovery time is unknown) there are 20 cases of interest, where the reporter has indicated that the sexual dysfunction has persisted for longer than one month after ceasing the drug (7 fluoxetine, 6 paroxetine, 4 citalopram, 2 escitalopram and 1 sertraline).

3.2. Consumer Group and Reports on Internet Forums

Consumer reports of persistent sexual side effects after discontinuation of medications are available on the Yahoo-SSRIsex internet community (<http://health.groups.yahoo.com/group/SSRIsex/>) (Bahrack 2006).

The MAH chose not to discuss the number of case reports on the site currently but it is estimated that there are more than 2100 members at the time of drafting this paper each reporting some persistence of sexual side effects since stopping a SSRI antidepressant. The nomenclature for suspected reactions and persistence definitions are highly variable. It is not clear how similar these cases are to the ones identified in the review by the MAH.

3.3. Incidental Research Findings

The MAH discusses the study by Montejo and colleagues previously presented in the November 2009 PEAG paper. This study, in which patients with SSRI-induced sexual dysfunction were switched to the dopaminergic antidepressant amineptine, reported that 55% of patients still had at least some type of sexual dysfunction after six months compared to 4% in the control group treated with amineptine alone.

3.4. Other Commentaries, Letters, and Reviews

Other commentaries, letters, and reviews have debated the topic of persistent sexual dysfunction following SSRI discontinuation, including doing epidemiological studies to find the prevalence and practical treatments (Farnsworth 2009). Persistent genital arousal disorder in women following discontinuation reviews have also been published (Goldmeier and Leiblum 2006; Goldmeier et al. 2009) in addition to a letter from a persistent sexual arousal internet support group member asking for awareness and studies in this population (Freed 2005).

4.1.5. Case Reports from the literature

Several case reports discussed in the November 2009 PEAG paper were included in this section by the MAH (citalopram [Csoka, 2008; Kauffman, 2007; Csoka, 2006; Adson, 2003], escitalopram [Leiblum, 2008; Adson, 2003], fluoxetine [Csoka, 2008; Leiblum, 2008; Csoka, 2006], paroxetine [Csoka, 2008; Leiblum, 2008], sertraline [Csoka, 2008; Leiblum, 2008; Bolton, 2006; Csoka, 2006]) and/or SNRI (milnacipran [Csoka, 2008], venlafaxine [Csoka, 2008; Leiblum, 2008]) discontinuation.

Those that discuss fluoxetine are summarized below:

4.1.5.1 Csoka et al. 2008 : 29-year-old male took 20 mg/day of fluoxetine at age 18 for 4 months (for anxiety and uncertainty related to career and academics). Before taking fluoxetine, patient never had problems getting erections. Within 3-4 days of initiating fluoxetine he became impotent at times and at others experienced delayed ejaculation along with weight loss, somnolence, and short-term memory problems but libido was not affected. Dose was increased to 40 mg/day after 2 months. The patient discontinued abruptly without problems but erectile dysfunction remains at the time of drafting this paper . No psychological or physical health problems found along with

normal blood work (testosterone, estrogens, prolactin, and glucose). Penile Doppler ultrasound showed good arterial blood flow in addition to there being no problems with the patient's spine. Patient takes 20 micrograms of alprostadil as needed for intercourse and maintains a long-term relationship.

The Author cites that 1300 individuals identified themselves as experiencing sexual dysfunctions after discontinuation of SSRIs on SSRIs internet community. Three cases were judged to be highly credible and were interviewed based on the internal consistency of their posting history to the group for over 2 years. The authors present several mechanistic hypotheses behind persistent sexual dysfunction after SSRI discontinuation: the role of downregulation of dopaminergic neurotransmission, peripheral changes due to inhibition of serotonin receptors in the peripheral nerves, neurological alterations in the areas of the nervous system responsible for sexual arousal and functioning, structural changes to brain regions involved in sexual response, and epigenetic changes caused by these medications.

The authors state that none of the patients discussed in this report received adequate informed consent with regards to the known risks of sexual side effects.

4.1.5.2: Csoka and Shipko 2006: 27-year-old female prescribed fluoxetine 20 mg/day for chronic insomnia, anxiety, and moderate depression after which sleep and mood were immediately improved. Within 3 days of therapy, dramatic loss of libido, marked reduction of genital and nipple sensitivity with concurrent anorgasmia were noted. Fluoxetine was discontinued after 7 months. Orgasmic capacity returned but at a dramatically reduced intensity and with a refractory period of several days, and tactile sensitivity only partially returned. Libido loss was reported as almost total, compared to very high libido since puberty. Serum testosterone and estradiol were normal.

Authors present several hypotheses regarding biochemical and neurochemical changes that occur during SSRI use that could account for their sexual side effects: transporter and receptor densities and cerebral gene expression normalize in most patients but there might be significant delays in some; negative feedback regulation of the hypothalamic-pituitary-testicular axis that does not fully normalize in some patients; persistent sexual side effects are caused by a similar mechanism to extrapyramidal effects but in area of the nervous system responsible for sexual function.

4.1.5.3: Leiblum and Goldmeier 2008: 60-year-old female developed persistent genital arousal disorder after having been on fluoxetine for many years for depression. Patient was switched to paroxetine, venlafaxine, sertraline, and escitalopram, but continued to have disabling genital arousal with each one. The patient chose to discontinue antidepressant medication and be depressed rather than endure the sensations.

Responses from an on-line internet survey of women complaining of persistent genital arousal disorder were reviewed.

Possible mechanisms for persistent genital arousal disorder were reviewed. The two main theories of aetiology of the phenomenon were cited as SSRI discontinuation increasing levels of atrial natriuretic peptide which induces cyclic guanosine

monophosphate and local vulval vasodilation and SSRI discontinuation magnifying the reduction in cortical and limbic responses.

4.1.6. *Persistent Sexual Benefits after Discontinuation*

Safarinejad and Hosseini (2006) evaluated citalopram as a treatment for premature ejaculation in a 12-week, prospective, double-blind, placebo-controlled, fixed-dose (20 mg/day), randomized study of 58 non-depressed, psychologically and physically healthy men whose only sexual complaint was premature ejaculation. Patients were evaluated every 2 weeks and in 3- and 6-month follow-up visits after discontinuation of treatment.

Significant ejaculation-delaying benefits in the citalopram study were sustained ($p < .001$) after citalopram discontinuation in both the 3- and 6-month assessments (Safarinejad 2006).

In another prospective, placebo-controlled crossover study of sertraline (50 mg/day) in 147 healthy men with premature ejaculation, ejaculation latency was measured during two 4-week treatment phases and monthly during a 6-month follow-up phase (Arafa 2006). Of the 126 men who achieved increased ejaculation latency during sertraline treatment, 100 were followed for 6 months after discontinuation.

Thirty-four (34) men reported good control over ejaculation while 66 men experienced relapse of premature ejaculation after sertraline discontinuation. The authors called for further large studies to evaluate sertraline's sustained effects on ejaculation latency, specifically after drug discontinuation.

4.0 Discussion

The totality of data presented by the MAH of fluoxetine are suggestive of an effect of fluoxetine on sexual functioning that has been reported by some patients to persist once treatment is discontinued. The details around the suspected adverse reaction are not clear and the data are considered too limited to definitively prove or exclude the association between prior fluoxetine exposure and the occurrence of sexual side effects that persist once medication is ceased. One of the major difficulties with investigating the phenomenon is the lack of a clear definition around the term 'persistent'.

The data from the spontaneous cases presented by the MAH lack detail necessary to thoroughly assess the association between the reported suspected adverse drug reactions and prior exposure to fluoxetine.

No one mechanistic theory can fully explain the reported effects and it is likely that a number of factors play a role in individual cases. The underlying illness that is the indication for treatment with fluoxetine is frequently associated with sexual dysfunction proving one of the most difficult confounders when assessing drug causality. The effects of the underlying illness on several putative PSSD aetiological theories and the possible lack of response to treatment are areas that require greater scientific understanding before we can attribute or rule out that the effects are due to the medication itself.

There are good preclinical studies showing that fluoxetine exposure in animals can affect reproductive function into the juvenile stage of development with permanent structural adverse changes to the reproductive organs of rats as presented in section 5.3 of the fluoxetine SPC.

Pre authorisation clinical trials for fluoxetine did not specifically capture data on persistence or remission of any sexual side effects occurring when patients ceased the medication. Discontinuation reactions were specifically studied but data on persistence of any sexual side effects on trial completion are not available.

Several SSRIs including citalopram, sertraline and fluoxetine have published clinical trials showing efficacy in the treatment of premature ejaculation. Dapoxetine is a short acting SSRI currently licensed for the indication of premature ejaculation in several member states and dapoxetine is undergoing assessment for the indication in the UK market via the mutual recognition procedure. It is likely that the effects on sexual function reported in association with fluoxetine are common to all members of the SSRI class.

The total of 93 cases identified from the fluoxetine spontaneous database containing 130 suspected adverse reactions relating to persistent sexual dysfunction following fluoxetine discontinuation have the limitations to interpretation of data common to all spontaneous reports. The MAH has classified only 9 reports as serious. In the assessment report provided by the MAH, even the serious suspected adverse drug reactions are not reported individually in detail and more information has been requested.

In summary, the data for the association of fluoxetine exposure with sexual dysfunction that persists on stopping the drug consist of some clear preclinical evidence of an effect of fluoxetine on reproductive systems in rats, 3 case reports from the literature, 93 reports of limited data content from the MAH including the 7 cases in the yellow card database where the reporter indicates the sexual dysfunction has persisted for longer than one month after stopping fluoxetine and a large number of case reports available on an internet forum set up for people reporting the phenomenon of PSSD.

It is recognised that providing complete information to patients and prescribers is important but equally it is important that this information is both helpful and evidence based. The current information in both the SPC and PIL for Prozac highlight that sexual dysfunction can occur in association with fluoxetine although the usefulness term “poor sexual performance” in adequately describing the difficulties in obtaining or maintaining an erection is questionable and more helpful descriptions of these side effects could be included in the PIL. The MAH has proposed to update the SPC and PIL in line with changes that have been made to the CCDS, which have essentially added a qualifying comment after the sexual dysfunction terms that occasionally they may persist after treatment discontinuation.

Addition of such a qualifying statement may not be helpful without quantification of how long the problem may persist and indeed if this may be permanent. The available

evidence does not allow us to determine for how long after treatment the problem may persist for or indeed how many people may experience persistent effects.

5.0 Conclusions

The data suggesting that sexual dysfunction associated with SSRIs may persist after treatment is discontinued is limited to individual case reports and complicated by the underlying medical condition being treated.

If persistent sexual dysfunction does occur we do not have any evidence which would allow us to determine the frequency or duration of this effect.

The available data do not support updates to the product information in relation to persistence of sexual dysfunction.

6.0 The Group's advice is sought on:

- the strength of the evidence that fluoxetine is associated with sexual side effects that can rarely persist in some patients after stopping the medicine?
- whether the risk should be labelled in the product information of fluoxetine and what, if any, updates to the fluoxetine PIL in particular are suggested?

References

1. Casper RC, Redmond E, Katz MM, Schaffer CB, Davis JM, Koslow SH. Somatic symptoms in primary affective disorders: presence and relationship to the classification of depression. *Arch Gen Psychiatry* 1985; 42: 1098–104
2. Bahrack AS. Post SSRI Sexual Dysfunction. American Society for the Advancement of Pharmacotherapy Tablet 2006;7:2-10.
3. Bahrack A. Persistence of Sexual Dysfunction Side Effects after Discontinuation of Antidepressant Medications: Emerging Evidence. *The Open Psychology Journal*, 2008, 1,42-50
4. Adson DE, Kotlyar M. Premature ejaculation associated with citalopram withdrawal. *Ann Pharmacother*. 2003;37(12):1804–1806.
5. Arafa M, Shamlous R. Efficacy of sertraline hydrochloride in treatment of premature ejaculation: a placebo-controlled study using a validated questionnaire. *Int J Impot Res*. 2006;18:164-169.
6. Bolton JM, Sareen J, Reiss JP. Genital anaesthesia persisting six years after sertraline discontinuation. *J Sex Marital Ther*. 2006;32(4):327–330.
7. Csoka AB, Bahrack AS, Mehtonen OP. Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors (SSRIs). *J Sex Med*. 2008;5(1):227–233.
8. Csoka AB, Shipko S. Persistent sexual side effects after SSRI discontinuation. *Psychother Psychosom*. 2006;75(3):187–188.
9. Farnsworth KD, Dinsmore WW. Persistent sexual dysfunction in genitourinary medicine clinic attendees induced by selective serotonin reuptake inhibitors. *Int J STD AIDS*. 2009;20(1):68– 69.
10. Freed L. Persistent sexual arousal. *J Sex Med*. 2005;2:743.
11. Goldmeier D, Mears A, Hiller J, Crowley T, BASHH Special Interest Group for Sexual Dysfunction. Persistent genital arousal disorder: a review of the literature and recommendations for management. *Int J STD AIDS*. 2009;20(6):373-377.
12. Goldmeier D, Bell C, Richardson D. Withdrawal of selective serotonin reuptake inhibitors (SSRIs) may cause increased atrial natriuretic peptide (ANP) and persistent sexual arousal in women? *J Sex Med*. 2006;3(2):376.

13. Goldmeier D, Leiblum SR. Persistent genital arousal in women -- a new syndrome entity. *Int J STD AIDS*. 2006;17(4):215–216.
14. Kauffman RP. Persistent sexual side effects after discontinuation of psychotropic medications. *Primary Psychiatry*. 2008;15:24.
15. Kauffman RP, Murdock A. Prolonged post-treatment genital anesthesia and sexual dysfunction following discontinuation of citalopram and the atypical antidepressant nefazodone. *The Open Women's Health Journal*. 2007;1:1–3.
16. Kennedy SH, Rizvi S. Sexual dysfunction, depression, and the impact of antidepressants. *J Clin Psychopharm*. 2009;29(2):157-164.
17. Leiblum SR, Goldmeier D. Persistent genital arousal disorder in women: case reports of association with anti-depressant usage and withdrawal. *J Sex Marital Ther*. 2008;34(2):150– 159.
18. Montejo AL, Llorca G, Izquierdo JA, Carrasco JL, Daniel E, Pérez-Sola V, Vicens E, Bousoño M, Sánchez-Iglesias S, Franco M, Cabezudo A, Rubio V, Ortega MA, Puigdemívol M, Domenech JR, Allué B, Sáez C, Mezquita B, Gálvez I, Pacheco L, de Miguel E. [Sexual dysfunction with antidepressive agents. Effect of the change to amineptine in patients with sexual dysfunction secondary to SSRI][Article in Spanish]. *Actas Esp Psiquiatr*. 1999;27(1):23-34.
19. Safarinejad MR, Hosseini SY. Safety and efficacy of citalopram in the treatment of premature ejaculation: a double-blind placebo-controlled, fixed dose, randomized study. *Int J Impot Res*. 2006;18:164-169.

